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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,177	12/31/2003	Andrew P. Levy	P-7339-US	7660
49443	7590	11/07/2006	EXAMINER	
PEARL COHEN ZEDEK, LLP PEARL COHEN ZEDEK LATZER, LLP 1500 BROADWAY 12TH FLOOR NEW YORK, NY 10036			GOLDBERG, JEANINE ANNE	
			ART UNIT	PAPER NUMBER
			1634	

DATE MAILED: 11/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/748,177.

Applicant(s)

LEVY, ANDREW P.

Examiner

Jeanine A. Goldberg

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 September 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,12-15,17 and 26-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,12-15,17 and 26-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 3/06.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 5, 2006. Currently, claims 1, 3, 12-15, 17, 26-28 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.
2. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Election/Restrictions

3. Applicant's election without traverse of Group II, Claims 1-5, 12-19, 26-28 in the paper filed November 28, 2005 is acknowledged.

The response to the restriction is made with traverse. The response asserts that upon allowance of the linking claims, the restriction requirement as to the linked inventions shall be withdrawn. This argument has been thoroughly reviewed and deemed persuasive. Upon allowance of a linking claim, the withdrawn claims which are linked by the linking claim will be rejoined.

Claims 6-11, 20-25, 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 6-11, 20-25, 29 drawn to an invention nonelected with traverse in the paper filed November 28, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Pages 48-54 contain a list of references which have not been considered as they have not been provided or cited on a 1449.

Response to IDS filed 3/24/06

The response indicates an IDS was filed on 3/24/06. The IDS indicates that the information cited on the IDS was cited by a foreign patent office within 3 months prior to filing the IDS or was not known to any individual designated in 1.56 within 3 months of filing the IDS.

The response asserts that the IDS was filed on March 24, 2006.

It does not follow that the statement on the IDS is consistent with the apparent facts of the case. Since the references were listed in the application on the filing date of

December 31, 2003 and in parent applications, it would not seem that the statement that they were not known prior to 3 months before the filing of the IDS would be correct.

Clarification is requested.

The IDS will not be considered at this time in view of the inconsistency on the record.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3, 12-15, 17, 26-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining a potential of a diabetic patient to benefit from vitamin E therapy for treatment of CV death or MI wherein the benefit from said vitamin E therapy to a patient having a haptoglobin 2-2 phenotype is greater compared to patients having haptoglobin 1-2 phenotype or 1-1 phenotype, does not reasonably provide enablement for a method of determining a potential of a diabetic patient to benefit from any anti oxidant therapy for treatment of any cardiovascular complication wherein the benefit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of determining a potential of a diabetic patient to benefit from anti oxidant therapy for treatment of a cardiovascular complication by determining a haplotype phenotype of the diabetic patient and thereby determining the potential of the diabetic patient to benefit from said anti-oxidant therapy.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the art

The art teaches the effect of vitamin therapy on the progression of coronary artery atherosclerosis varies by haptoglobin type in postmenopausal women (Levy et al. *Diabetes Care*, Vol. 27, No. 4, pages 925-930, April 2004). Levy teaches that changes in the MLD as a function of haptoglobin phenotype and vitamin therapy were analyzed. The analysis of changes in LDL and HDL levels with and without vitamin therapy were analyzed in diabetic patients. The LDL levels in Diabetic patients was not significantly different between vitamin and placebo treated (see Table 4).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification and Working Examples

The specification provides no evidence that the broad scope of the claims are enabled. The specification has analyzed vitamin E and Ramipril which are deemed to be two particular anti-oxidant therapies. The specification teaches there is a 100% concordance between the haptoglobin phenotype as determined from plasma and the haptoglobin genotype as determined from genomic DNA by the PCR. As seen in Table

5 of the instant specification (page 45), the analysis based on DM patients only did not provide a statistically significant result for Hp 2-2 phenotype for stroke when treated with vitamin E. Table 6 illustrates that in diabetic patients the Hp 2-2 phenotype is not associated with CV death, MI or Stroke. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention as broadly as claimed.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

The claims are broadly drawn to any cardiovascular complication, however, the specification fails to provide a significant association between CV, MI or stroke. Given the guidance in the instant specification it is clear that the skilled artisan would not be able to use the presence of the Hp 2-2 phenotype as indicative of CV, MI or stroke. The non-significant p-values provided for the analysis in the specification do not support a method for determining a potential of a diabetic patient to benefit from oxidant therapy. While the skilled artisan could provide additional experimentation to determine whether a subgroup of the population, or another population may have an association between hp 2-2 phenotype and all cardiovascular diseases, the results are unpredictable, since three of the four complications studied did not yield positive associations.

Furthermore, given the analysis in the specification of vitamin E and Ramipril, there is no predictable correlation between Hp 2-2 phenotype and greater benefit for anti oxidant therapy. Diabetic patients with CV death and MI appear to be significantly associated with vitamin E. However, diabetic patients provided Vitamin E showed no

association with stroke. The association pattern for Ramipril is different. CV death, MI and Stroke each do not appear to be significantly associated with Hp 2-2 phenotype in diabetics. Based upon the different patterns, the administration of one anti-oxidant therapy would not be indicative of each other anti-oxidant therapy. For example, since Vitamin E and Ramipril each have different associations, it would be unpredictable whether Vitamin C, for example, would be associated with anti oxidant therapy benefits. The specification does not provide any analysis for diabetic retinopathy, nephropathy or neuropathy, for example. Therefore, it would be unpredictable whether either Vitamin E, Vitamin C or Ramipril would be associated with Hp 2-2 phenotype and benefits from anti-oxidant therapy.

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art do not provide a reliable association between anti oxidant therapies and benefits to cardiovascular complications in diabetic patients. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems for association studies. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of

guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the Examiner's concern with regard to the complications has been addressed. This argument has been considered but is not convincing because the specification teaches a lack of association in several cardiovascular conditions, including CV, MI or stroke.

While, the prior applications, including 6,613,519 may point out that the haptoglobin 2-2 is an inferior antioxidant, the instant specification does not appear to support the broad scope of the instant claim for determining the diabetic patients to benefit from any oxidant therapy for treatment of any cardiovascular disease. The response does not appear to address any of the negative teachings in the art or the specification which are discussed in the rejection above.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

6. No claims allowable.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

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Jeanine Goldberg
Primary Examiner
October 27, 2006